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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/235,875	01/22/1999	LARA MADISON	MBX020	2296

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EXAMINER	
KALLIS, RUSSELL	
ART UNIT	**PAPER NUMBER**
1638	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/235,875	MADISON ET AL.	
	Examiner	Art Unit	
	Russell Kallis	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,7,10 and 14-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,7,10 and 14-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 June 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

The disclosure is objected to because of the following informalities: On page 21, line 25, the *A. caviae* PHB polymerase gene referenced in (Fukui & Doi, *J. Bacteriol.* 179: 4821-30 (1997)) is incorrect. The *A. caviae* polymerase gene referenced in Fukui & Doi is a PHA synthase encoded by a phaC gene not a PHB gene.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 7, 10 and 14-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The added claimed material which is not supported by the original disclosure is as follows: Newly amended Claim 1 recites "a phbC polymerase gene that encodes an enzyme that polymerizes 3-hydroxybutyryl CoA and 3-hydroxyhexanoyl-CoA". There is no support in the specification for a *phbC* polymerase gene encoding an enzyme that polymerizes hydroxybutyryl

CoA and 3-hydroxyhexanoyl-CoA. The specification supports PHB polymerases from *Z. ramigera* that have a strict specificity for 3-hydroxy butyryl CoA and a PHB polymerase from *R. eutropha* that is highly specific for the 3-hydroxybutyryl CoA monomer and has shown a 7.5% activity towards 3-hydroxyvaleryl CoA, but there is no support in the specification for a *phbC* polymerase that polymerizes 3-hydroxybutyryl CoA and 3-hydroxyhexanoyl CoA. There is only speculation that the *phbC* gene from *N. salmonicolor* encodes a PHB polymerase that might have a wider substrate range than the other PHB biosynthetic enzymes on page 12 lines 1-6, but there is nothing that asserts that there is an isolated phbC gene encoding an enzyme that polymerizes 3-hydroxybutyryl CoA and 3-hydroxyhexanoyl-CoA. Applicant is invited to point to the page and line number in the specification where support can be found. Absent of such support, Applicant is required to cancel the new matter in the reply to this Office Action.

Claims 1, 6, 7, 10 and 14-21 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for the reasons of record set forth in the Official action mailed 12/9/2002, 6/3/2003 and 11/19/2003. Applicant's arguments filed 2/3/2004 have been considered but are not deemed persuasive.

Claims are drawn to a method for the biological production of polyhydroxyalkanoate containing 3-hydroxyhexanoate, comprising growing a transgenic bacterium transformed with phbA, phbB, and phbC genes. The enzymes set forth in the claims are; a phbA thiolase gene, a phbB reductase gene, a phbC polymerase gene encoding an enzyme that polymerizes 3-

hydroxybutyryl CoA and 3-hydroxyhexanoyl CoA; a gene encoding a β-hydroxyacyl-ACP-coenzyme A transferase, a D-specific enoyl-CoA hydratase, a thiolase specific for 3-ketohexanoyl CoA, a reducatase specific for 3-ketohexanoyl and one or more fatty acid biosynthethic enzymes.

Applicant asserts that the materials required to practice the invention are known and that what is actually being claimed are new combinations of those materials (response pages 20-23). Applicant does not describe the composition or structure for any of the genes of the generic functional categories of bacterial enzymes set forth in the claims. Since the specification only provides a characterization of what the genes do, rather than their structural features it is unclear whether the inventor had possession of the claimed invention at the time of filing of the application. Applicant has not described a representative number of sequences encoding the various enzymes of the invention nor has there been a description of conserved regions that would define any of those broadly claimed categories of genes encoding the enzymes of the invention so that one would know that one was in possession of the claimed invention.

Claims 1, 6, 7, 10 and 14-21 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of production of a polyhydroxyalkanoate containing 3-hydroxyhexanoate, by growing a bacterium transformed with a phaC gene from *A. caviae*, a phbA from *R. Eutropha* and a phbB gene from *R. Eutropha*; or by growing a bacterium transformed with a phaB gene from *R. Eutropha* and a phaJ gene from *A. caviae*, does not reasonably provide enablement for a method of production of a polyhydroxyalkanoate containing 3-hydroxyhexanoate, comprising providing a bacteria

expressing a phbA thiolase gene, a phbB reductase gene, and a phbC polymerase gene encoding an enzyme that polymerizes 3-hydroxybutyryl CoA and 3-hydroxyhexanoyl CoA; further comprising a gene encoding a β-hydroxyacyl-ACP-coenzyme A transferase; or further comprising a phaJ gene encoding a D-specific enoyl-CoA hydratase; or further comprising the genes encoding the enzymes of Claim 17; or further comprising expressing genes encoding one or more fatty acid biosynthetic enzymes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. This rejection is maintained for the reasons of record set forth in the Official action mailed 12/9/2002, 6/3/2003 and 11/19/2003. Applicant's arguments filed 2/3/2004 have been considered but are not deemed persuasive.

Applicant claims a method of production of a polyhydroxyalkanoate containing 3-hydroxyhexanoate, comprising providing bacteria expressing a phbA thiolase gene, a phbB reductase gene, and a phbC polymerase gene encoding an enzyme that polymerizes 3-hydroxybutyryl CoA and 3-hydroxyhexanoyl CoA; a method further comprising a gene encoding a β-hydroxyacyl-ACP-coenzyme A transferase; or a method further comprising a phaJ gene encoding a D-specific enoyl-CoA hydratase; or a method further comprising the genes encoding the enzymes of Claim 17; or a method further comprising expressing genes encoding one or more fatty acid biosynthetic enzymes.

Applicant teaches PHBH synthesis from butyrate in *E. coli* transformed with genes encoding PHA synthase from *A. caviae* (*phaC*), and β-ketoacyl-CoA reductase (*phbB*) and β-ketothiolase (*phbA*) from *R. Eutropha* (example 2); PHBH synthesis using a Fatty Acid Oxidation pathway in *E. coli* transformed with genes encoding D-specific enoyl-CoA hydratase

from *A. caviae* (*phaJ*), and 3-ketohexanoyl-CoA reductase (*phbB*) from *R. Eutropha* (example 4); production of PHBH copolymers from butanol in *E. coli* expressing genes encoding PHA synthase from *A. caviae* (*phaC*), and β-ketothiolase (*phbA*) and β-ketoacyl-CoA reductase (*phbB*) from *R. Eutropha* (example 5).

Applicant does not teach a method of biological production of a polyhydroxyalkanoate, containing 3-hydroxyhexanoate by growing transgenic bacteria expressing comprising providing bacteria expressing a phbA thiolase gene, a phbB reductase gene, and a phbC polymerase gene encoding an enzyme that polymerizes 3-hydroxybutyryl CoA and 3-hydroxyhexanoyl CoA; a method further comprising a gene encoding a β-hydroxyacyl-ACP-coenzyme A transferase; or a method further comprising a phaJ gene encoding a D-specific enoyl-CoA hydratase; or a method further comprising the genes encoding the enzymes of Claim 17; or a method further comprising expressing genes encoding one or more fatty acid biosynthetic enzymes.

Further, there is no support for isolated genes encoding a β-hydroxyacyl-ACP-coenzyme A transferase or a D-specific enoyl-CoA hydratase. The specification merely indicates organisms from which those genes might possibly be isolated on page 5 lines 22-25. Furthermore, previously presented Claim 7 recites *phbC* polymerase genes from *Aeromonas caviae, Comamonas testosteroni, Thiocapsia pfenigii, Chromatium vinosum, Bacillus cereus, Nocardia Carolina, Nocardia salmonicolor, Rhodococcus rubber, Rhodococcus rhodocrous,* and *Phodospirilum rubrum*. The specification only supports a *phbC* polymerase gene from *Nocardia salmonicolor* on page 12, lines 11-12.

Applicant asserts that that it is not important to know the sequences encoding the enzymes of the invention but what is important is to know a source and what the genes must

encode because the activity of the gene can be transferred from one organism to another without knowing the sequence, and since Applicants provide the source of the activity and both the PCR methods for isolating a gene of interest and for testing the activity, the claims are enabled (response pages 14-18). Applicant's specification does not provide support for a phbC polymerase gene encoding an enzyme that polymerizes 3-hydroxybutyryl CoA and 3-hydroxyhexanoyl CoA. The specification only supports a *phbC* polymerase gene from *Nocardia salmonicolor* on page 12, lines 11-12. Further, See *Genentech, Inc. v. Novo Nordisk, A/S*, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that disclosure of a "mere germ of an idea does not constitute [an] enabling disclosure", and that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention. Furthermore, See *In re Fisher,* 166 USPQ 18, 24(CCPA 1970) which teaches "That paragraph (35 USC 112, first) requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved."

Isolation of gene homologues from different bacterial organisms is highly unpredictable and requires significant guidance with respect to the probes, primers, hybridization and wash conditions and/or PCR reaction conditions. For example, in Boynton *et al.* (J. of Bacteriol. Vol.

178: 3015-3024, 1996), page 3021 column 1 lines 31-40, and column 2 lines 1-4, the authors show the degree of amino acid identity between crotonase, from *C. acetobutylicum*, compared to *C. difficile,* and *E. coli* to be 41% and 34% respectively. Furthermore, an analogous comparison of *eftA* and *eftB* genes from *C. acetobutylicum* and *P. denitrificans*, two of the microorganisms chosen as inventions in the specification, shows 30% and 36% amino acid sequence identity. The difference in nucleotide sequence identity, based upon the differences in amino acid identity, would introduce unpredictability in isolating the genes of the invention, other than those described in the examples. Based on the unpredictability in the art, the limited guidance set forth in the specification, and the breadth of the claims, one of average skill would have to resort to undue experimentation to work out the PCR conditions and primers to enable the invention.

Metabolic engineering of microorganisms or plants with non-native bacterial enzymes is highly unpredictable. The unpredictability arises from a lack of understanding of both the complex interactions of non-native protein assembly and the perturbation of regulation within the transgenic that may arise when engineered changes to metabolic pathways introduce novel interactions (De Luca, V., Ag Biotech News and Information. 1993 Vol. 5, No. 6, pp. 225N-229N) (page 225N, column 2, lines 6-8). Boynton *et al.* (J. of Bacteriol. Vol. 178: 3015-3024, 1996) show, (page 3021, Discussion, lines 17-22) that *C. acetobutylicum* butyryl Co-A dehydrogenase (BCD) activity was not detected in transformed *E. coli* extracts when grown under aerobic or anaerobic conditions. Since the gene is present, the authors suggest that the enzyme is not functional in *E. coli* due to improper folding or is down regulated due to an unexpected autoregulatory control.

Considering the limited guidance in the specification showing bacterial production of PHA in *E. coli*, when compared to the broad palette of genes to be taken from the many different bacterial organisms and to be expressed in different species of bacteria as set forth in the claims, undue trial and error experimentation would be required to screen through cDNA and genomic clones, testing both genes and bacteria transformed with different genes and gene combinations to identify those genes that could be successfully used in the claimed method of producing PHA containing 3-hydroxyhexanoate in bacteria.

Given the lack of guidance, the limited working examples in the specification that reflect the breadth of the claims, and the unpredictability in the art, undue trail and error would be needed to practice the invention throughout the full scope of the claims. Therefore, the invention is not enabled for the scope set forth in the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is indefinite because "the three enzymes from *C. acetobutylicum*" and "the thiolase specific for 3-ketohexanoyl CoA" lack antecedence. Appropriate correction is required.

All claims are rejected.

Claims 1, 6, 7, 10 and 14-24 are deemed free of the prior art given the failure of the prior art to teach or reasonably suggest a method of biological production of a polyhydroxyalkanoate, containing 3-hydroxyhexanoate by growing transgenic bacteria comprising providing bacteria

expressing a phbA thiolase gene, a phbB reductase gene, and a phbC polymerase gene encoding an enzyme that polymerizes 3-hydroxybutyryl CoA and 3-hydroxyhexanoyl CoA; a method further comprising a gene encoding a β-hydroxyacyl-ACP-coenzyme A transferase; or a method further comprising a phaJ gene encoding a D-specific enoyl-CoA hydratase; or a method further comprising the genes encoding the enzymes of Claim 17; or a method further comprising expressing genes encoding one or more fatty acid biosynthetic enzymes.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (571) 272-0798. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Russell Kallis Ph.D.
April 28, 2004

ASHWIN D. MEHTA, PH.D
PATENT EXAMINER